Remarks/Arguments

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 119-131 were pending in this application and are rejected on various grounds. Claims 119-123 now recite the functional recitation "wherein said polypeptide induces chondrocyte redifferentiation" support for which is also found in the instant specification in Example 159, page 530. Claim 128 has been canceled without prejudice or disclaimer and claims 132-133 have been added which recite the functional recitation "wherein the nucleic acid encoding said polypeptide is amplified in adenocarcinomas or squamous cell carcinomas of the lung or in adenocarcinomas of the colon," support for which is found in the instant specification, in Example 170. Further, all pending claims have been amended to remove references to "Figures". The rejections to the presently pending claims are respectfully traversed.

Formal Matters

The title of the invention has been amended to describe, more particularly, what the Applicants consider is their invention. Entry of this amendment is respectfully requested.

IDS

Applicants submit an IDS separately enlisting references recited in the Blast report in order to be compliant with 37 C.F.R. § 1.98(a)(1). Consideration of this Information Disclosure Statement is respectfully requested.

Priority

The nucleic acid sequence of SEQ ID NO: 228 and the polypeptide of SEQ ID NO: 229 were first disclosed in U.S. provisional application 60/096,768, filed August 17, 1998, hence Applicants are entitled to an effective filing date of **August 17, 1998,** at least for the sequences of SEQ ID NO: 228 and SEQ ID NO: 229. This provisional application also discloses a utility for PRO1111 based on homology to LIG-1, a protein having leucine rich repeats. A copy of this provisional application is attached with this response for the Examiner's convenience.

Applicants rely on the 'gene amplification' assay (Example 143) for patentable utility of the subject matter relating to claims 119-123. This utility was first disclosed in the US

Provisional Application 60/141,037, filed June 23, 1999, priority for which has been claimed in this application. Hence, the present application is at least entitled to an effective filing date of **June 23, 1999** based on results of the 'gene amplification' assay. A copy of the relevant pages from this provisional application are attached for the Examiner's convenience.

Further, Applicants rely on the 'chondrocyte proliferation' assay (Example 153) for patentable utility of the subject matter relating to claims 119-123. This utility was first disclosed in International Application PCT/US00/08439, filed March 30, 2000, priority for which has been claimed in the instant application. Hence, the present application is at least entitled to an effective filing date of **March 30, 2000** based on results of the 'chondrocyte proliferation' assay. A copy of the relevant pages from this provisional application are attached for the Examiner's convenience.

The Examiner has acknowledged utility for the claimed protein and antibodies based on the chondrocyte redifferentiation assay. As per the Examiner's request, Applicants have provided a copy of the relevant portion of the PCT application, whose specification is identical to the instant application, that contains the chondrocyte redifferentiation assay for priority determination.

The Examiner further indicates that the gene amplification assay was not found to be enabling as required by the 35 U.S.C.§ 112, first paragraph. The Examiner indicates that the amplification was "mild" and also says that "a slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid". The Examiner quotes an exemplary reference like Sen and concludes that "the data was not corrected for aneuploidy". The Examiner further quotes Haynes *et al.,* Pennica *et al.* and Konopka *et al.* to show that "an increase in nucleic acid copy number is not predictive of a similar association for protein." For the reasons provided below, Applicants respectfully disagree.

Regarding the rejection on lack of correction of data based on aneuploidy, Applicants submit that, as noted by the Examiner and the Sen article, aneuploid tissues are cancerous or pre-cancerous. The present invention is directed to proteins and antibodies useful in the detection of cancer, irrespective of the mechanism by which gene amplification occurs. Even if aneuploid tissues were to predict a propensity for cancer, the instant proteins and antibodies are still useful

as diagnostic tools. Applicants have included a declaration by Avi Ashkenazi, Ph.D., a co-inventor of this application, who says that:

> "An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes."

Further, regarding the Examiner's rejection that "an increase in nucleic acid copy number is not predictive of a similar association for protein," Applicants first argue the teachings of the articles cited by the Examiner and provide exemplary articles to support their position that, it is more likely than not that amplified DNA results in amplified protein levels, barring certain exceptions.

Pennica *et al.* teaches that "An analysis of *WISP*-1 gene amplification and expression in human colon tumors **showed a correlation between DNA amplification and over-expression**, ... In contrast, *WISP*-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression in normal colonic mucosa from the same patient." (Emphasis added). The Applicants draw attention to Pennica's showing that "a correlation between DNA amplification and over-expression exists for the *WISP*-1 gene"in 84% of the tumors examined. While Pennica discloses a lack of correlation for the *WISP*-2 gene, Pennica teaches nothing regarding such a lack of correlation in genes <u>in general</u>. That is, Pennica's teachings are specific for the *WISP* family of genes, and are not directed to genes in general. The Utility Guidelines requires that for a *prima facie* showing of lack of utility, the Examiner has to provides evidence that it is **more likely than not** that a lack of correlation between protein expression and gene amplification exists, <u>in general</u>. Accordingly, Applicants respectfully submit that Pennica teaches nothing of the correlation between gene amplification and polypeptide over-expression in general.

Regarding the Examiner's rejection based on Konopka *et al.*, again, Applicants respectfully submit that the Examiner has generalized a result pertaining to merely **one** gene, the *abl* gene, to cover all genes <u>in general</u>. Konopka does not disclose any generalized teaching

about the correlation between protein expression and gene amplification. Applicants submit that the Konopka reference is not sufficient to establish such a *prima facie* showing of lack of utility based on the results with the *abl* gene alone. Thus, the combined teachings of Pennica and Konopka are not directed towards genes in general but to single genes or genes within a family and thus, their teachings have been misrepresented in this rejection.

Regarding Haynes, the Examiner says that "Haynes *et al.* studied 80 proteins... and found no strong correlation between proteins and transcript levels." Applicants respectfully traverse and point out that, on the contrary, Haynes teaches that "**there was a general trend** but no strong correlation between protein [expression] and transcript levels" (Emphasis added). Haynes studied 80 *yeast* proteins to show that "protein levels cannot be **accurately** predicted from the level of the corresponding mRNA transcript" (Emphasis added) (see page 1863, paragraph 2.1, last line). For example, in Figure 1, there is a positive correlation between mRNA and protein amongst **most** of the 80 yeast proteins studied but the correlation is "not linear" and hence, "one cannot **accurately** predict protein levels from mRNA levels." In fact, very few data points deviated or scattered away from the expected normal or showed a lack of correlation between mRNA: protein levels. Thus, the Haynes data meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein.

In conclusion, the Examiner has not shown that a lack of correlation between gene amplification: polypeptide over-expression, as observed for the *WISP-2* or the *abl* genes, is typical. In fact, contrary to what the Examiner contends, the art indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will be expressed at an elevated level. As noted even in Pennica *et al.*, a correlation between DNA amplification: polypeptide over-expression was observed in the case of *WISP-1* and similarly, in Haynes *et al.*, **most genes** showed a correlation between increased mRNA : translated protein. Since the standard is not absolute certainty, a *prima facie* showing of lack of utility has not been made in this instance.

It is "more likely than not" for amplified genes to have increased mRNA and protein levels

Applicants submit further exemplary articles to show that, contrary to what the Examiner asserts, just as in Haynes, the art indicates that, generally, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will be expressed at an elevated level. For example, Ornoft *et al.* (Mol. and Cell. Proteomics, 2002, Vol.1, pages 37-45) studied transcript levels of 5600 genes in malignant bladder cancers many of which were linked to the gain or loss of chromosomal material using an array-based method. Ornoft *et al.* showed that there was a gene dosage effect and taught that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* (Cancer Res., 2002, Vol. 62, pages 6240-45) showed, using CGH analysis and cDNA microarrays which compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there was "evidence of a prominent global influence of copy number changes on gene expression levels." (see page 6244, column 1, last paragraph). Additional supportive teachings were also provided by Pollack *et al.,* (PNAS, 2002, Vol. 99, pages 12963-12968) who studied a series of primary human breast tumors and showed that "...62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that in general, gene amplification increases mRNA expression.

In addition, enclosed is a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene

transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology, that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the vast majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Thus, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1111 gene, that the PRO1111 protein is concomitantly overexpressed. Thus, Applicants submit that the PRO1111 proteins have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use the protein and its antibodies for the diagnosis of cancer.

Claimed proteins would have diagnostic utility even if the protein were not overexpressed

Even assuming *arguendo* that, there is no correlation between gene amplification and increased mRNA/protein expression for PRO1111, which Applicants submit is not true, a polypeptide encoded by a gene that is amplified in lung or colon squamous cell carcinomas or adenocarcinomas would **still** have a credible, specific and substantial utility. In support, Applicants submit a Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the instant application. Dr. Avi Ashkenazi's Declaration explains that:

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Applicants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician need not treat a patient with agents that target that gene product. This not only saves money, but further prevents unnecessary exposure of the patient to the side effects of gene product targeted agents.

This is further supported by the teachings of the attached article by Hanna and Mornin. The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu

gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

In conclusion, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO1111 polypeptide based on the gene amplification results for the nucleic acid, for example, in detecting over-expression or absence of expression of PRO1111. In fact, the art also indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will also be expressed at an elevated level. Based on these discussions, one skilled in the art, at the time the application was filed, would know how to use the claimed polypeptides, without undue experimentation.

Thus, Applicants have demonstrated utility for the PRO1111 polypeptide and its antibodies based on the gene amplification assay and thus, Applicants request that the Examiner reconsider the priority date for the present application based on the present arguments.

Claim Rejections – 35 USC § 112, first paragraph -enablement

Claims 119-123 and 130-131 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for the protein of SEQ ID NO:229 or fragments thereof for making antibodies or having chondrocyte redifferentiation activity, does not reasonably provide enablement for proteins 80, 85, 90, 95 or 99% identity, which do not have chondrocyte redifferentiation activity.

As discussed above, Applicants have amended claims 119-123 with the functional recitation: "wherein said polypeptide induces chondrocyte redifferentiation." The Examiner has already acknowledged enablement for these claims based on the chondrocyte redifferentiation assay. The dependency of Claims 130 and 131 has been amended to claim 124 and hence these claims are obviated. Furthermore, new claims 132-133 recite the functional recitation "wherein the nucleic acid encoding said polypeptide is amplified in adenocarcinomas or squamous cell carcinomas of the lung or in adenocarcinomas of the colon." Arguments for patentable utility based on the gene amplification assay have been presented above, hence Applicants believe that the rejections to these claims should be obviated.

Accordingly, this rejection should be withdrawn.

Claim Rejections - 35 USC § 112, first paragraph -written description

Claims 119-124, 126-128 and 130-131 are rejected under 35 U.S.C. 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time of filing.

As discussed above, Applicants have amended claims 119-123 with the functional recitation: "wherein said polypeptide induces chondrocyte redifferentiation." The Examiner has already acknowledged enablement for claims 119-123 based on the chondrocyte redifferentiation assay. Furthermore, new claims 132-133 recite the functional recitation "wherein the nucleic acid encoding said polypeptide is amplified in adenocarcinomas or squamous cell carcinomas of the lung or in adenocarcinomas of the colon." Arguments for patentable utility based on the gene amplification assay have been presented above. Further, Example 14 of the Written Description Guidelines issued by the U.S. Patent Office which clearly states that "protein variants meets the requirements of 35 U.S.C.§112 first paragraph as providing adequate written description for the claimed invention even if the specification contemplates but does not exemplify variants of the protein if (1) the procedures for making such variant proteins is routine in the art, (2) the specification provides an assay for detecting the functional activity of the protein and (3) the variant proteins possess the specified functional activity and at least 95% sequence identity to the reference sequence". Based on these guidelines, Applicants submit that the instant specification evidences the actual reduction to practice of a full-length native human PRO1111 polypeptide of SEQ ID NO: 229, with or without its signal sequence and of the nucleic acid of SEQ ID NO: 228. In addition, the specification provides detailed description about the cloning of variants and describes the gene amplification assay for testing nucleic acids in a PCR based assay. Thus, Applicants submit that the genus of nucleic acids that code for the polypeptide of SEQ ID NO: 229 or variants of nucleic acid of SEQ ID NO: 228 with 95% similarity and further, which possess the functional property that it is "wherein the nucleic acid encoding said polypeptide is amplified in adenocarcinomas or squamous cell carcinomas of the lung or in adenocarcinomas of the colon" would encompass a genus that meets the requirements of 35 U.S. C. §112, first paragraph as providing adequate written description.

Hence, Applicants request that the present rejection be reconsidered and withdrawn.

Deposit requirement

Applicants submit amendments to the specification regarding the ATCC deposit incorporating the requisite assurances that the Examiner required. Accordingly, Applicants request that this rejection be withdrawn.

Claim Rejections – 35 USC § 102

Claims 119-123 and 130-131 are rejected under 35 U.S.C. §102(a) or (b) as being anticipated by Jacobs et al. (WO 99/50405, pub date 10/7/99).

As discussed under priority, the PRO1111 sequence and its encoding nucleic acid were first disclosed in U.S. Provisional application 60/096,768, filed **8/17/1998**, priority to which has been claimed in the instant application. This provisional application also discloses a utility for PRO1111 based on homology to LIG-1, a protein having leucine rich repeats. Furthermore, as discussed earlier, specific, substantial and credible utilities for PRO1111 have been asserted by Applicants at least on **October 23, 1999** based on the gene amplification assay and at least on **March 30, 2000** for the chondrocyte proliferation utility. Since the date for reduction to practice for the PRO1111 sequences **(8/17/1998)** precedes the publication date of Jacobs *et al.*, Jacobs is not prior art under 35 U.S.C. § 102(a) or (b) and hence this rejection should be withdrawn.

Claims 119-124, 127-128 and 130-131 are rejected under 35 U.S.C. §102(e) as being anticipated by Shimkets et al. (U.S. patent, 6,689,866 dated 3/8/00).

As discussed above, Applicants are at least entitled to an effective filing date of **June 23, 1999** based on the results of the 'gene amplification' assay for Claims 119-124 and 127-128 and 130-131. Therefore, Shimkets is not prior art. Therefore, this rejection should be withdrawn.

Claim Rejections – 35 U.S.C. §103(a)

1) Claims 119-123 and 130 are rejected under 35 U.S.C. §103(a) as being obvious over any one loci AI769814, AI435407, AI470931 or T15752 in view of Sibson et al.

2) Claim 131 is rejected under 35 U.S.C. §103(a) as being obvious over any one loci AI769814, AI435407, AI470931 or T15752 in view of Sibson et al. and further in view of USPN 5,116,964 (Capon).

Again, as discussed above, Applicants are at least entitled to an effective filing date of **August 17, 1998** for the protein and nucleic acid sequences of SEQ ID NOs: 229 and 228, respectively, and further, Applicants are at least entitled to an effective filing date of **June 23, 1999** based on the results of the 'gene amplification' assay. Further, Applicants submit that ESTs AI769814, AI435407, AI470931 or T15752 are not enabling disclosures since they do not

provide any utility. Therefore, Applicants submit that ESTs AI769814, AI435407, AI470931 or T15752 are not prior art.

Since the primary references are not 103(a) references, and Sibson does not teach SEQ ID NOs: 229 nor 228 of the instant application, this rejection falls and should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C17). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: November 8, 2004

Daphne Reddy

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